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EDITORIAL COMMENT

The Pulse of Cardiology

Quo Vadis?*

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The value of new analytical techniques is increasingly recognized in cardiology. These may be statistical (1) or mathematical (2) and permit new information to be extracted from data, which are readily available or can be collected easily. An example is analysis of the pulse waveform, which can easily be measured by tonometry at the wrist or in the neck (3). At present, the pulse is only utilized for measurement of heart rate, or through estimation of its peak and nadir as systolic and diastolic blood pressure, respectively. Yet, the pulse is known to contain key information, and its waveform was first used to identify elevated blood pressure and to chart the natural history of essential hypertension well over a century ago (4) and to identify the therapeutic effect of glyceryl trinitrate (5)—all well before clinical introduction of the now ubiquitous brachial cuff.

See pages 695 and 705

New pulse wave developments in the understanding of aging, heart failure, and hypertension have appeared in the *Journal* recently, with 2 articles in the current issue. The first (6) deals with arterial wave reflection and genetic influences in women, the second with the effects of drugs and heart rate on central systolic arterial pressure and its derivation from brachial pulse waves (7). For clinicians to benefit from the studies, it is desirable to provide background and to summarize development of this field of pulse waveform analysis.

The Brachial Cuff and Brachial Pressures

The cuff sphygmomanometer was introduced by Riva Rocci in 1896 to measure systolic pressure by palpation, with the auscultatory Korotkov method introduced in 1905 for measurement of diastolic pressure (8,9). Neither method was or could be calibrated against intra-arterial pressure at the time, and it was only after 50 years that studies showed that the Riva Rocci and Korotkov techniques usually underestimated brachial systolic pressure and overestimated diastolic pressure, even when phase 5 (sound disappearance) was used (10). Nonetheless, sphygmomanometry, due to its simplicity of use and widespread application, continues to provide strong prognostic information. Using the Framingham study data, diastolic pressure was shown to be the best predictor of events under age 40 years, systolic the best predictor over age 40 years, and pulse pressure (systolic − diastolic) the best predictor over age 60 years (11–13). These views have been supported by modern data, although they challenged the seemingly irrefutable older data on 1 million subjects who were followed up in decades past (14).

Arterial Tonometry and Arterial Pressure Waves

The first sphygmograms, used to record the pulse waveform by Mahomed and Marey (4,8,15), were mechanical devices and difficult to use (9,10). It is small wonder that they were swept aside by the brachial pressure cuff in the early 1900s. Since then, arterial applanation tonometry has become widely used and shown to be accurate in recording the shape of the pressure wave in different arteries (3) and the further changes that occur with aging and with drug therapy. Studies with arterial models and in patients at cardiac catheterization showed that the upper limb arteries (between ascending aorta and wrist) could be characterized in the frequency domain by a transfer function, which was similar in adult humans and changed little with aging, disease, and drugs (16–18). This transfer function permitted the central aortic pressure waveform to be generated from the radial pulse waveform (10,16). When calibrated to the sphygmomanometer for systolic and diastolic pressure, one could calculate the central aortic systolic, diastolic, and pulse pressure (19). In large studies, central pressures were found to be more robust than brachial pressures at predicting events in epidemiological and drug trials (20,21), heralding the next era of blood pressure management.

Factors that affect the relationship between the peripheral arterial pressure waveform and the central waveform are becoming more widely appreciated both in healthy (6) and in hypertensive populations (7). In studies of central pressure, interest has focused on the waveform and the factors that influence this (10,22). The most obvious factor is ventricular ejection, which creates the initial part of the wave; this travels over the arterial tree to the peripheral arterioles, where there is an abrupt increase in impedance at the arteriolar level. Steady flow is generated in the arterioles and the wave is reflected, and travels back to the heart as an echo of the initial wave. This reflected wave is superimposed on the initial wave; thus, the pressure wave in an artery characteristically has 2 peaks (whereas ascending aortic flow has just 1 peak) (10,22). In young adults, the reflected wave returns to the heart at the end of systole, and boosts

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coronary flow throughout diastole. In older persons, as a consequence of arterial stiffening, the wave travels faster and returns earlier and forms a secondary wave during late systole. The ill effects of aging can be seen as augmentation of late systolic pressure, as well as increase in amplitude of the primary wave (23).

In clinical studies, the influence of proximal aortic stiffness can be gauged by the amplitude of the initial wave in the aortic pulse, and the ill effect of wave reflection can be gauged by the degree of pressure augmentation (23). Pressure augmentation is a manifestation of the ill effect of wave reflection increasing pulsatile afterload, as previously characterized by vascular impedance (24). Basic principles of arterial hemodynamics are provided in textbooks and reviews (8,10,19,22,23). Pulse waveforms can be analyzed in the frequency and the time domains, and must provide identical information on wave travel and reflection. Yet, there is considerable controversy in the field, especially with respect to aging changes, and the relevance of wave reflection and its modification by drugs. New outcome information is beginning to emerge from the Framingham study, which has been measuring arterial pulse waves in its present cohort for over a decade (25,26).

Heritability and Wave Reflection

The first paper in this issue of the *Journal* (6) uses measurements of ascending aortic pressure waveforms, with the SphygmoCor device (AtCor Medical, Sydney, Australia), together with carotid-femoral ("aortic") pulse wave velocity and measurement of proximal aortic, abdominal aortic, and femoral artery diameter in a large group of women from the Twins UK registry. Cecelja et al. (6) used amplitude of the primary wave (P1) to represent pressure generated by ventricular ejection and amplitude of the central augmented wave (cAP) as an indication of wave reflection, and expressed augmentation index (AIx) as AP/(P1 + AP). As had others (27), they found cAP and AIx to be highly hereditable. They found a close relationship between P1 and aortic pulse wave velocity, as one would expect. They also demonstrated a strong inverse relationship between arterial tapering with wave reflection, consistent with basic hemodynamic theory of differences in regional vascular impedance. Height was not included in the multiple regression analysis, despite its well-known relationship with augmentation and with wave reflection (27,28). The very strong heritability previously shown for height (27) may have gone a long way to explaining the heritability demonstrated in the current study.

Study results were seen by authors to differ from those reported by Mitchell et al. (25) for the Framingham results and Segers et al. (29) for the large European Asklepios cohort. On the basis of their work, Mitchell et al. (25) have argued that change in aortic stiffness rather than of wave reflection is responsible for change in central aortic pressure with aging. Others, including ourselves (30,31), see this differently, with wave reflection predominant, but being manifest as a boost to late systolic pressure or reduction in late systolic flow in older subjects (32). This area is complex, but should be resolved by longitudinal data, which will come from the Framingham and Asklepios investigators.

Heart Rate and Wave Reflection

In this issue of the *Journal*, Williams and Lacy (7) expand their analysis of the CAFE (Conduit Artery Function Evaluation) study (21) in order to examine how use of atenolol led to a higher central systolic pressure than did amlodipine for the same change in systolic brachial pressure. The CAFE study was a substudy of the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) study (33), which showed superiority of amlodipine over atenolol in reducing cardiovascular events. Results of the CAFE study explained benefit on the basis of greater reduction in central than brachial systolic pressure with amlodipine. Williams and Lacy (7) sought to find whether the lesser benefit of atenolol in the CAFE study came directly from the drug, or as a consequence of reduction in heart rate. Their conclusion was that reduction of heart rate was the major contributor to the difference seen in the CAFE study. The difference between brachial and aortic systolic was found to vary between 4 mm Hg at a heart rate of 45 beats/min and 20 mm Hg at a heart rate of 110 beats/min. The difference can be expressed as lesser amplification at low heart rates, and greater amplification at higher heart rates.

Results are convincing, but not entirely surprising. Data were plotted over the range of 45 to 110 beats/min or 0.75 to 1.9 Hz. The transfer function used in the same SphygmoCor device used by Cecelja et al. (6) shows substantial amplification between these frequencies (34), and substantially more between 1.5 and 3.0 Hz, which corresponds to the second harmonic of the pressure wave. Amplification is at its peak (of 2.5- to 3-fold) at around 4 Hz. Further, Taylor (35) emphasized that wave reflection depends on frequency, as a consequence of physical dispersion of peripheral reflection sites, and varies between around 80% at very low frequencies (<1 Hz in man) to zero at higher frequencies (>10 Hz). This was demonstrated in dogs by Alexander et al. (36) in 1989. Amplification of the compound wave is shown to vary substantially also with heart rate (37), with values similar to those reported by Williams and Lacy (7). Reading their report, skeptics might be tempted to say that the major disadvantage of atenolol is that it reduced heart rate, and that if heart rate remained unchanged, amlodipine would have shown no advantage. But amlodipine and other dihydropyridines do reduce wave reflection, and this is manifest as a reduction in augmentation index and augmentation of the aortic pressure wave, and is seen independently of heart rate when ascending aortic impedance is displayed in the frequency domain (38,39). The studies by Ting et al. (40) quoted by authors

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showed such behaviors for impedance with nifedipine, nitroprusside, and angiotensin-converting enzyme inhibitors, but not diuretics (41), without a change in heart rate. The authors suggested that low heart rate may be disadvantageous, and were hard pressed to explain benefits of bradycardia in trained athletes at rest. Trained athletes usually have lower wave reflection as a consequence of greater peripheral arterial vasodilation, attributed to improved endothelial function (10,42). It is well known that heart rate is a risk factor for cardiovascular disease (43)—so the general proposition does not hold.

The authors also discuss the lesser value of beta-blocking drugs, particularly those which reduce heart rate, on stroke, and attribute this to greater wave reflection. We see this as quite probable, and based on the view of "pulse wave encephalopathy" when the pulsatile component of flow is increased in the cerebral microvasculature (44,45). Flow pulsations are increased in the internal carotid artery when wave reflection is increased at slow heart rates (46), correlate with increased pressure augmentation in this vessel (45), and can be reduced by an arterial dilating drug (47). The possibility that beta-blockers enhance wave reflection (i.e., the reflection coefficient) due to reflex vasoconstriction is not really discussed. This raises the possibility that vasodilating beta-blockers may not have the same effects. Similarly, sinus node inhibitors devoid of vascular activity such as ivabradine may not have such an adverse effect. It should be re-emphasized that the population under study is a hypertensive cohort, and that beta-blockers remain one of the cornerstones of therapy for chronic systolic heart failure and in the early post-infarction population.

So where is this field heading? It stands to reason that the 2 techniques used clinically in the past (study of the pulse and studies from the cuff) can be combined to better characterize left ventricular load and to understand the effects of drugs and of disease. We have been confused and misled in the past by overinterpretation of brachial diastolic pressure as the "sine qua non" for definition of hypertension. We have been misled by systolic brachial pressure, finding that this can be 20 mm Hg or more (80 mm Hg during exercise) (10) greater than aortic and left ventricular systolic pressure. The least accurate part of estimating central aortic pressure is the measurement of cuff pressure—particularly diastolic pressure (48), rather than measurement of the pulse by applanation tonometry at the wrist—or even in the neck from the carotid arteries. Further studies may show that measures that do not depend on the cuff, such as AIx or amplification between aorta and radial artery, may be superior to measurements that depend on cuff values. This has already been suggested in small studies for regression of left ventricular hypertrophy in hypertension (49) and for development of cerebral lacunar infarcts (45,46).

The ubiquitous brachial cuff sphygmomanometer has changed only cosmetically since its introduction over a century ago, in the era of the Wright Brothers' conquest of the skies. It needs be supplemented, and better use of the arterial pulse is a logical path. This view endorses that of Frederick Mahomed when, as a 23-year-old medical student, he addressed a meeting at Guy's Hospital London and said, "The pulse ranks first among our guides; no surgeon can despise its counsel, no physician shut his ears to its appeal. Since then the information the pulse affords is of so great importance, and so often consulted, surely it must be to our advantage to appreciate fully all it tells us, and to draw from it all that it is capable of imparting."

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